Complete Summary

GUIDELINE TITLE

Practice guidelines for the management of patients with histoplasmosis.

BIBLIOGRAPHIC SOURCE(S)

Wheat J, Sarosi G, McKinsey D, Hamill R, Bradsher R, Johnson P, Loyd J, Kauffman C. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):688-95. [46 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Histoplasmosis

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide recommendations for treating patients with the more common forms of histoplasmosis

TARGET POPULATION

Patients with histoplasmosis

INTERVENTIONS AND PRACTICES CONSIDERED

Antifungal therapy

- Ketoconazole
- Itraconozole
- Fluconazole
- Amphotericin B
- Liposomal amphotericin B
- Amphotericin B colloidal suspension
- Amphotericin B lipid complex

MAJOR OUTCOMES CONSIDERED

- Eradication or chronic suppression of infection
- Resolution of clinical abnormalities
- Prevention of relapse

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Grades reflecting the quality of evidence on which recommendations are based:

I. Evidence from at least one properly randomized, controlled trial

II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

A working group of 8 experts in the field was convened to develop this guideline. The working group developed and refined the guideline through a series of conference calls.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of recommendation:

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation
D. Moderate evidence to support a recommendation against use
E. Good evidence to support a recommendation against use

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

Each recommendation includes a ranking for the strength and the quality of evidence supporting it. Definitions of the levels of evidence (I-III) and grades of recommendation (A-E) are repeated at the end of the Major Recommendations field.

Indications for antifungal treatment in patients with histoplasmosis

Treatment indicated

- Acute pulmonary histoplasmosis with hypoxemia
- Acute pulmonary histoplasmosis for >1 month
- Chronic pulmonary histoplasmosis
- Esophageal compression and/or ulceration
- Granulomatous mediastinitis with obstruction and/or invasion of tissue
- Disseminated histoplasmosis

Treatment not indicated

- Acute self-limited syndromes
- Acute pulmonary histoplasmosis, mildly ill
- Rheumatologic
- Pericarditis
- Histoplasmoma
- Broncholithiasis
- Fibrosing mediastinitis*

*Note: Antifungal therapy has not been proven effective for this form of histoplasmosis but should be considered, especially in patients with elevated erythrocyte sedimentation rates or complement fixation titers $\geq$1:32.

Acute Pulmonary Histoplasmosis

Fever, chills, headache, myalgia, anorexia, cough, and chest pain characterize this form of histoplasmosis and are seen in 85%–100% of cases. Patients may experience pleuritic pain. The findings on examination are usually unremarkable, except for fever, but may include rales or pleural friction rubs.

The course after low-level exposure is benign in immunocompetent patients. Symptoms usually abate within a few weeks of onset. Therapy may be helpful in symptomatic patients whose conditions have not improved during the first month of infection. Fever persisting for >3 weeks in acute histoplasmosis may indicate that the patient is developing progressive disseminated disease, which may be aborted by therapy. Whether antifungal therapy hastens recovery or prevents complications is unknown, since it has never been studied in prospective trials.

Patients with diffuse radiographic involvement following more intense exposure often experience more severe disease. They may become hypoxemic and even require ventilatory support. Without treatment, recovery is usually slow and the outcome may be fatal.

Localized pulmonary histoplasmosis

Treatment is not indicated in the typical patient with acute pulmonary histoplasmosis because the illness is self-limited and associated with minimal morbidity (EIII). Treatment with itraconazole, 200 mg once daily for 6–12 weeks, should be considered for patients who have shown no clinical improvement after 1 month of observation (BIII). Blood concentrations of itraconazole obtained 2–4 hours after administration of a dose could be monitored in selected situations: suspected treatment failure, concern about compliance or absorption, use of medications that may reduce the solubility of itraconazole or accelerate its metabolism, and desire to reduce the dose from 200 mg twice daily to 200 mg once daily. Although the "therapeutic" concentration has not been defined, the MIC_{90} of itraconazole for Histoplasma capsulatum is 0.02 micrograms/mL, which suggests that serum concentrations of 1 microgram/mL measured by bioassay should be therapeutic. Among patients with acquired immune deficiency syndrome (AIDS), the median plasma concentration was about 6 micrograms/mL for patients receiving a dosage of 200 mg twice daily and ~ 3 micrograms/mL for those receiving 200 mg once daily.

Diffuse pulmonary histoplasmosis in an immunocompetent host

Amphotericin B, 0.7 mg/kg/day (or 1 of the lipid preparations at a dose of 3 mg/kg/day for patients with renal impairment) should be used initially in those patients with more severe manifestations who require ventilatory supportive therapy (AIII). If amphotericin B is used exclusively because the patient cannot be treated with oral medications, a total course of less than or equal to 35 mg/kg is recommended, but this situation is expected to be rare (AIII).

The inflammatory response may contribute to the pathogenesis of the respiratory compromise; thus, corticosteroids may be helpful, and prednisone could be administered at a dosage of 60 mg daily for 2 weeks (CIII). The role of corticosteroids for treating extensive pulmonary histoplasmosis in the immunocompromised host is less clear. Patients with AIDS and concurrent disseminated histoplasmosis and Pneumocystis carinii pneumonia who received corticosteroids in conjunction with treatment for both microbial pathogens did not appear to do more poorly than other patients treated with antifungal therapy only.

After discharge from the hospital, itraconazole, 200 mg once or twice daily, should be used to complete a 12-week course (BIII).

Itraconazole alone, 200 mg once or twice daily for 6-12 weeks, could be used for patients who are not sufficiently ill to require hospitalization (BIII).

Chronic Pulmonary Histoplasmosis

Patients with underlying lung disease may develop chronic pulmonary infection after exposure to Histoplasma capsulatum. The clinical and radiographic findings resemble those seen in reactivation tuberculosis. Without treatment, the illness is progressive, causing loss of pulmonary function in most patients and death in up to half. In 1 study, although only 30% of cases progressed after 1 year, 79% progressed with longer observation. Although some patients improve spontaneously, they remain at risk for recrudescence.

Treatment is indicated in all patients with chronic pulmonary histoplasmosis. Studies have shown amphotericin B to be effective in 59%–100% of cases. Ketoconazole and itraconazole are effective in 75%–85% of case patients, but their use is also complicated by high relapse rates. Fluconazole, 200–400 mg daily, appears to be less effective (64% response) than ketoconazole or itraconazole. Itraconazole, 200 mg once or twice daily for 12–24 months, is the treatment of choice for chronic pulmonary histoplasmosis (AII).

Amphotericin B, 50 mg daily, or about 0.7 mg/kg/day, is recommended for patients who are judged to require hospitalization because of ventilatory insufficiency or general debilitation, inability to take itraconazole because of drug interactions or allergies, inability to absorb itraconazole, inability to achieve detectable concentrations of itraconazole in the blood, or failure to improve clinically after at least 12 weeks of itraconazole therapy (AII). Some patients may not be able to tolerate that dosage of amphotericin B, which justifies reducing the dosage to 0.5-0.6 mg/kg/day or to use 1 of the lipid formulations. If amphotericin B is administered for the full course of therapy, at least 35 mg/kg should be given at doses of 50 mg 3 times weekly, if tolerated. In most patients, however, treatment can be changed to itraconazole, 200 mg once or twice daily.

Fluconazole, 200-400 mg daily, is less effective than amphotericin B or itraconazole and yielded a response rate of 64% in 1 study. Fluconazole could be used in patients who cannot receive itraconazole or are unable to achieve detectable blood concentrations with itraconazole, but the dose should be increased to 400–800 mg daily (BII). In a study of patients with AIDS who had disseminated histoplasmosis, 800 mg daily was used for histoplasmosis.

Ketoconazole (200 mg, 400 mg, or 800 mg daily) is reasonably effective but less well-tolerated than itraconazole or fluconazole. Toxicity is more common in patients receiving the 800 mg daily dosage, which is discouraged.

Disseminated Histoplasmosis

Underlying immunosuppressive conditions and extremes of age are risk factors for dissemination, and illness is more severe in immunocompromised individuals. Fever and weight loss are the most common symptoms, and hepatomegaly or splenomegaly are common physical findings of disseminated histoplasmosis. Other frequent sites of dissemination include the oropharyngeal or gastrointestinal mucosa, the skin, and the adrenal glands. Shock, respiratory distress, hepatic and renal failure, and coagulopathy may complicate severe cases. Central nervous system (CNS) involvement occurs in 5%–20% of cases, presenting as chronic meningitis or focal brain lesions. Histoplasma rarely infects the spinal cord. The mortality without treatment is 80% but can be reduced to <25% with antifungal

therapy. Treatment is indicated for all patients with progressive disseminated histoplasmosis.

In studies that mostly included immunocompetent hosts and specifically excluded those with AIDS, amphotericin B was effective in 68%–92% of patients, itraconazole (200–400 mg daily) in 100% (only 10 patients studied), ketoconazole (200–400 mg daily) in 56%–70%, and fluconazole (200–400 mg daily) in 86%.

Among patients with AIDS, therapy with amphotericin B was effective in 74%–88% of patients, itraconazole (400 mg daily for 12 weeks) in 85%, ketoconazole (200–400 mg daily) in 9% (only 11 cases), and fluconazole (800 mg daily for 12 weeks) in 74%. Of note, patients with severe or moderately severe clinical manifestations were excluded from the prospective studies that used itraconazole and fluconazole but not from the retrospective reviews of patients treated with amphotericin B. Of patients with severe disease, nearly half died despite treatment with amphotericin B, whereas 98% of those with less severe illness responded to therapy.

There are no published reports about the use of the newer lipid preparations of amphotericin B for treating histoplasmosis. Most patients respond to therapy rapidly, with resolution of fever in 1–2 weeks. Therapy is not curative for patients with AIDS. Lifelong maintenance therapy is needed to prevent relapse in patients with AIDS and disseminated histoplasmosis. Amphotericin B, 50 mg given weekly or twice weekly, is highly effective (81%–97%) but inconvenient and not well-tolerated. Itraconazole, 200–400 mg daily, was effective in at least 90% of cases. Fluconazole, 100–400 mg daily was effective maintenance therapy in 88% of patients with AIDS who received amphotericin B induction therapy. However, in a prospective study, relapse occurred in nearly one-third of patients who received fluconazole, 400 mg daily, after successful induction therapy with fluconazole, 800 mg a day. In vitro resistance to fluconazole developed in isolates from about half of those patients who relapsed.

Immunocompetent hosts and immunocompromised hosts without AIDS.

Amphotericin B, 0.7–1.0 mg/kg/day is recommended for patients who are sufficiently ill to require hospitalization (See Table 2 of the original guideline document for specific dosing recommendations) (AII). Experience using the lipid formulations of amphotericin B for treating histoplasmosis has not been reported. Most patients respond quickly to amphotericin B and can then be treated with itraconazole. The transition from amphotericin B to itraconazole therapy could occur after the patient becomes afebrile, no longer requires blood pressure or ventilatory support or intravenous fluids or nutrition, and is able to take oral medications. If amphotericin B is to be used for the full course, the total dosage should be 35 mg/kg given over 2–4 months.

Itraconazole, 200 mg once or twice daily for 6–18 months, is the treatment of choice for patients with mild or only moderately severe symptoms who do not require hospitalization, and for continuation of therapy in those whose condition has improved in response to amphotericin B (AII).

Fluconazole should be used only in patients who cannot take itraconazole (BII). The fluconazole dosage should be at least 400 mg daily in

nonimmunocompromised individuals and 800 mg daily in those with severe immunosuppressive conditions. Histoplasma capsulatum may develop resistance to fluconazole during therapy, leading to relapse and thus necessitating careful follow-up assessment, including measurement of Histoplasma capsulatum antigen concentration in blood and urine (BIII).

Ketoconazole, 200 mg once or twice daily, is also reasonably effective (56%–70% response rate) but less well-tolerated than itraconazole or fluconazole. Ketoconazole could be used in some situations where itraconazole is contraindicated (BII).

Antigen testing may be useful for monitoring therapy in patients with disseminated histoplasmosis. Most of the data on the use of the antigen test for monitoring therapy are derived from studies of patients with AIDS. Antigen concentrations decrease with therapy and increase with relapse. Some investigators recommend that treatment should be continued until antigen concentrations revert to negative or at least reach low levels of less than or equal to 4 units. If treatment is stopped before antigen concentrations in urine and serum revert to negative, patients should be followed closely for relapse, and antigen levels should be monitored every 3–6 months until they become negative (BIII).

Patients with AIDS as the cause of immunosuppression

Therapy is divided into an initial 12-week intensive phase to induce a remission in the clinical illness and then followed by a chronic maintenance phase to prevent relapse. A similar approach may be appropriate in other patients without AIDS who have relapsed after appropriate courses of therapy.

For induction therapy, amphotericin B is recommended for patients who are sufficiently ill to require hospitalization (See Table 2 of the original guideline document for specific dosing recommendations) (AII). Amphotericin B can be replaced with itraconazole, 200 mg twice daily (when the patient no longer requires hospitalization or intravenous therapy), to complete a 12-week total course of induction therapy.

Itraconazole, 200 mg 3 times daily for 3 days and then twice daily for 12 weeks is the treatment of choice for patients who have mild or moderately severe symptoms who do not require hospitalization (AII).

Fluconazole, 800 mg daily, is an alternative for patients who cannot take itraconazole (BII). Patients who are receiving fluconazole should be followed closely clinically for relapse, and antigen concentrations in urine and blood should be monitored quarterly and at the time of suspected relapse (BIII).

For maintenance therapy, the treatment of choice is itraconazole 200 mg once or twice daily for life (AII). Antigen concentrations in serum and urine should be monitored every 3–6 months to provide evidence that maintenance therapy is continuing to suppress the progression of infection (BIII).

Amphotericin B, 50 mg intravenous once weekly, is an alternative but is not as well-tolerated or accepted by patients and should be reserved for patients who cannot take itraconazole (BII).

Fluconazole, 400–800 mg daily, could be used for patients who cannot tolerate or do not absorb itraconazole and prefer not to be treated with amphotericin B, but fluconazole therapy is discouraged because of its reduced efficacy as chronic maintenance therapy for histoplasmosis (DII). Patients receiving fluconazole should be followed closely clinically for relapse, and antigen concentrations in urine and blood should be monitored quarterly and at the time of suspected relapse.

For prophylaxis in immunocompromised subjects, itraconazole is recommended. A trial comparing itraconazole, 200 mg daily, versus placebo in patients with CD4+ counts <150/microliters showed a 2-fold reduction in the incidence of histoplasmosis in the itraconazole group, compared with the placebo group (6.8%–2.7%) during a median follow-up period of 1 year.

In regions experiencing high rates of histoplasmosis (>5 cases/100 patient-years), prophylaxis with itraconazole is recommended (200 mg once daily) (BI). Fluconazole is not an acceptable alternative because of its inferior activity against Histoplasma capsulatum, and lower efficacy for treatment of histoplasmosis.

Central Nervous System (CNS) Histoplasmosis

Manifestations include meningitis, focal brain or spinal cord lesions, cerebrovascular accident caused by vascular involvement or cerebral emboli, and diffuse encephalitis. Symptoms usually have been present for months to years before diagnosis. Fever, headache, confusion, mental status changes, seizures, or focal neurological deficits may be seen. Cerebral spinal fluid abnormalities include lymphocytic pleocytosis, protein elevation, and hypoglycorrhachia in patients with meningitis. Single or multiple enhancing lesions may be seen by computed tomography (CT) scan or magnetic resonance imaging (MRI) in the brain or spinal cord of those with parenchymal involvement.

The course of the disease is progressive and fatal if not treated, although the speed of clinical deterioration is highly variable. The response to therapy is inferior to that in other types of histoplasmosis: 20%–40% of patients with meningitis succumb to the infection, despite treatment with amphotericin B, and up to half of responders relapse after therapy is discontinued.

The optimal treatment for Histoplasma meningitis is unknown, but an aggressive approach is recommended because of the poor outcome.

Amphotericin B, 0.7–1 mg/kg/day to complete a 35 mg/kg total dose over 3–4 months has been used most often (BIII). Fluconazole, 800 mg daily, might be continued for another 9–12 months after completion of amphotericin B, to reduce the risk for relapse (BIII).

Liposomal amphotericin B, 3–5 mg/kg/day or every other day given over a 3–4 month period might be considered for patients who have failed therapy with

amphotericin B followed by fluconazole (CIII). In animal studies, liposomal amphotericin B achieved higher concentrations in the blood and brain than did amphotericin B or the other lipid formulations, which provides a theoretical basis for its use in meningitis. However, neither the lipid preparation nor amphotericin B achieve detectable concentrations in cerebral spinal fluid, and none have been evaluated in cases of Histoplasma meningitis.

Chronic fluconazole maintenance therapy, 800 mg daily, should be considered for patients who relapse, despite full courses of therapy, as described elsewhere (CIII).

Itraconazole, although more active than fluconazole against Histoplasma capsulatum, does not enter the cerebral spinal fluid, which makes it a less-appealing choice for treatment of meningitis and discourages its use for this indication (DIII). Of note, however, the role of cerebral spinal fluid concentrations of antifungal agents in the outcome of treatment of fungal meningitis is unclear.

Patients who relapse despite chronic maintenance therapy are candidates for administration of amphotericin B directly into the ventricles, cisterna magna, or lumbar arachnoid space. Experience using intrathecal or intraventricular therapy, however, has not been encouraging; this approach to therapy is discouraged except for patients for whom all other approaches to therapy have failed (DIII).

Focal involvement of the brain or spinal cord in the absence of meningitis may be more responsive to antifungal therapy. Of 6 such cases in persons without AIDS, all responded to amphotericin B therapy, but 2 relapsed. Amphotericin B is recommended for the initial therapy (BIII). Penetration of the cerebral spinal fluid may not be required for successful therapy of parenchymal lesions; thus itraconazole, 200 mg 2 or 3 times daily, may be appropriate after the patients´ conditions have improved with amphotericin B (CIII).

Parenchymal lesions rarely require surgical excision (DIII).

Granulomatous Mediastinitis

Symptoms that include chest pain, cough, hemoptysis, and dyspnea may be caused by compression of the airways, superior vena cava, or pulmonary vessels in patients with granulomatous mediastinitis. These syndromes represent active inflammation of the mediastinal lymph nodes rather than fibrotic reactions to past infection. Although symptoms are often mild and resolve over a few months, they may be more severe and protracted. Antifungal therapy has been helpful in some cases. Adjunctive treatment with corticosteroids appeared to have been beneficial in 1 patient who had airway obstruction. Resection of obstructive masses is another approach that has been helpful for patients with granulomatous mediastinitis.

Amphotericin B, 0.7–1.0 mg/kg/day, should be considered as initial therapy for patients with severe obstructive complications of mediastinal histoplasmosis (BIII). Therapy could be changed to itraconazole, 200 mg once or twice daily, after improvement is sufficient for outpatient treatment.

Itraconazole, 200 mg once or twice daily for 6–12 months, is recommended for patients with milder manifestations that persist for >1 month (BIII).

Prednisone, 40–80 mg daily for 2 weeks, could be considered in those with major airway obstruction (CIII).

Surgical resection of the mediastinal mass should be reserved for patients who remain symptomatic and continue to demonstrate obstruction of major mediastinal structures, despite a trial of antifungal therapy (BIII).

Fibrosing Mediastinitis

Fibrosing mediastinitis is a late complication of histoplasmosis arising from nodal regions and ultimately invasion and occlusion of the central vessels and airways. Patients often report symptoms of several years´ duration at the time of diagnosis. The course is progressive and often fatal. Although most authorities believe that neither antifungal nor anti-inflammatory treatment ameliorates the outcome of fibrosing mediastinitis, others have reported improvement after antifungal therapy.

Information is inadequate on which to make firm treatment recommendations. The progressive course of this syndrome, however, makes it difficult to withhold antifungal therapy. If the clinical findings are consistent with a more acute inflammatory process rather than a chronic fibrotic process, especially if complement fixation titers and the erythrocyte sedimentation rate are elevated, treatment may be helpful.

A 12-week trial of itraconazole, 200 mg once or twice daily, is suggested if clinical findings do not differentiate fibrosing mediastinitis from granulomatous mediastinitis (CIII). Patients who truly have fibrosing mediastinitis are not expected to respond to antifungal therapy. The only basis to prolong therapy beyond 12 weeks would be clearcut radiographic demonstration of abatement of obstruction, in which case therapy could be continued for 1 year.

Corticosteroid therapy has not been helpful when tried and is discouraged (DIII).

Surgery should be approached with great caution in patients with severe complications of fibrosing mediastinitis and only in those who are expected to succumb from the condition without intervention. Surgeons experienced in the management of fibrosing mediastinitis should be consulted (CIII).

Placement of intravascular stents has been helpful in some patients with superior vena cava, pulmonary artery, or pulmonary vein obstruction, and might be tried in patients with severe manifestations (CIII).

Pericarditis

Pericarditis occurs in 5%–10% of patients with acute histoplasmosis and appears to be caused by the inflammatory response to the infection rather than the infection per se. These manifestations rarely may be a complication of disseminated histoplasmosis. Patients with pericarditis respond to non-steroidal

anti-inflammatory agents without antifungal therapy, but those with pericardial tamponade often require percutaneous or surgical drainage of the pericardial fluid. Long-term outcome is excellent, with only rare progression to constrictive pericarditis.

Antifungal therapy is not recommended (DIII).

Therapy with nonsteroidal anti-inflammatory agents is recommended for 2–12 weeks, on the basis of clinical resolution of the symptoms and physical findings of pericarditis (BIII).

Corticosteroids might be tried for 1–2 weeks in patients with hemodynamic compromise, followed by continued treatment with nonsteroidal anti-inflammatory agents, until the clinical findings and radiographic evidence of cardiomegaly resolved (CIII). Concurrent itraconazole, 200 mg once or twice daily for 12 weeks, could be given along with corticosteroids, to reduce the concern that corticosteroids might promote progression of the infection (CIII).

Percutaneous or surgical drainage is recommended for patients with more severe findings of pericardial tamponade or with moderately severe evidence of hemodynamic compromise that does not respond to corticosteroids (AIII).

There is no evidence that antifungal, anti-inflammatory, or surgical therapy prevents constrictive pericarditis (DIII).

Rheumatologic Syndromes

The arthritis is polyarticular and symmetrical in half of cases and involves joints of the upper and lower extremities with similar frequency. Nearly half of patients with rheumatologic manifestations exhibit erythema nodosum and/or erythema multiforme. The joint symptoms usually resolve in response to treatment with nonsteroidal anti-inflammatory agents.

Antifungal therapy is not recommended (DIII).

Therapy with nonsteroidal anti-inflammatory agents is recommended for 2–12 weeks, on the basis of resolution of the symptoms and physical findings of arthritis and erythema nodosum (BIII). Relapse may occur after anti-inflammatory therapy is stopped, thus requiring reinstitution for another 4–8 weeks.

Histoplasmosis During Pregnancy

Pregnant women with histoplasmosis should not be treated with azole antifungal agents because of the potential of this class of drugs to cause teratogenic complications. Amphotericin B, however, is safe during pregnancy and is the treatment of choice for such cases. The safety of the lipid preparations of amphotericin B during pregnancy is unknown. There is no evidence that histoplasmosis is more severe during pregnancy or that dissemination occurs to the fetus.

Definitions of Strength of Recommendation and Quality of Evidence Ratings:

Quality of evidence:

I. Evidence from at least one properly randomized, controlled trial
II. Evidence from at least one well-designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results of uncontrolled experiments
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Strength of recommendation:

A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation
D. Moderate evidence to support a recommendation against use
E. Good evidence to support a recommendation against use

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

Controlled trials have been conducted that address the treatment of chronic pulmonary and disseminated histoplasmosis, but clinical experience and descriptive studies provide the basis for recommendations for other forms of histoplasmosis.

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Certain forms of histoplasmosis cause life-threatening illness and result in considerable morbidity, whereas other manifestations cause no symptoms or minor self-limited illnesses. The nonprogressive forms of histoplasmosis, however, may reduce functional capacity, affecting work capacity and quality of life for several months. Treatment is clearly beneficial and cost-effective for patients with progressive forms of histoplasmosis. The nonprogressive forms of histoplasmosis, however, may reduce functional capacity, affecting work capacity and quality of life for several months. It remains unknown whether treatment improves the outcome for patients with the self-limited manifestations, since this patient

population has not been studied. Other chronic progressive forms of histoplasmosis are not responsive to pharmacologic treatment.

Subgroups Most Likely to Benefit:

Patients with progressive forms of histoplasmosis, such as chronic pulmonary or disseminated infection.

POTENTIAL HARMS

Antifungal Therapy

- Conventional amphotericin B is associated with significant toxicity, including infusion-related events, such as chills, fever, headache, nausea and vomiting, and dose-limiting nephrotoxicity.
- Lipid formulations of amphotericin B, although offering several therapeutic advantages over conventional amphotericin B, are considerably more expensive, ranging from 10- to 20-fold higher in cost.
- One potential limitation of the azole antifungal drugs is the frequency of their interactions with coadministered drugs, which results in adverse clinical consequences. One type of azole-drug interaction may lead to decreased plasma concentration of the azole, related to either decreased absorption or increased metabolism of the azole. A second type of azole-drug interaction may lead to an unexpected toxicity of the coadministered drug, relating to the ability of the azoles to increase plasma concentrations of other drugs by altering hepatic metabolism via the cytochrome P-450 system.
- A second potential limitation of the azoles is the emergence of resistance of fungal organisms, especially Candida species, to fluconazole.
- Patients receiving ketoconazole, especially in the large 800 mg. daily dose are at risk for toxicity.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Wheat J, Sarosi G, McKinsey D, Hamill R, Bradsher R, Johnson P, Loyd J, Kauffman C. Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. Clin Infect Dis 2000 Apr;30(4):688-95. [46 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000 Apr

GUIDELINE DEVELOPER(S)

Infectious Diseases Society of America - Medical Specialty Society

SOURCE(S) OF FUNDING

Infectious Diseases Society of America (IDSA)

GUIDELINE COMMITTEE

Infectious Diseases Society of America (IDSA) Practice Guidelines Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Authors: Joe Wheat, George Sarosi, David McKinsey, Richard Hamill, Robert Bradsher, Phillip Johnson, James Loyd, and Carol Kauffman

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Infectious Diseases Society of America (IDSA) Web site. Also available in HTML format.

Print copies: Available from the University of Chicago Press; fax: (773) 702-6096.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Kish MA. Guide to development of practice guidelines. Clinical Infectious Diseases 2001;32:851-4.
- Gross PA. Practice guidelines for infectious diseases: Rationale for a work in progress. Clin Infect Dis. 1998 May;26(5):1037-41.
- Gross PA, Barrett TL, Dellinger EP, Krause PJ, Martone WJ, McGowan JE Jr, Sweet RL, Wenzel RP. Purpose of quality standards for infectious diseases. Infectious Diseases Society of America. Clin Infect Dis 1994 Mar;18(3):421.

Electronic copies: Available from the Infectious Diseases Society of American (IDSA) Web site.

Print copies: Available from Infectious Diseases Society of America, 66 Canal Center Plaza, Suite 600, Alexandria, VA 22314.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on May 1, 2001. The information was verified by the guideline developer as of June 29, 2001.

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